NOS: 11 and 12. Claims 13 and 15 recite that the plant cell is a monocot and a dicot, respectively. Support for these claims can be found, for example, on page 10, lines 19-21. Claim 14 recites that the monocot is maize. Support for this claim can be found throughout the specification. See, for example, Example 1 and 2.

Claims 16-29 have been added. Newly submitted claims 16-29 mirror claims 1-15 except that they are directed to a method for inactivating a gene introduced into the genome of a plant. Support for these claims can be found throughout the specification and in the originally filed claims.

No new matter has been added by way of these amendments. Reexamination and reconsideration of the amended and newly submitted claims is requested.

Amendments to the Specification

The specification has been amended to correctly reference the SEQ ID NOS present in the sequence listing. No new matter has been added by way of these amendments. Applicants submit the specification is now in compliance with 37 C.F.R. 1.821-1.825.

Amendments to the Sequence Listing

The sequence listing has been amended to include SEQ ID NOS: 14-29. SEQ ID NOS: 14-21 comprise oligonucleotides set forth on pages 17-20 of the specification. SEQ ID NOS: 22-29 are set forth in Figures 1-13 of the specification. No new matter has been added by these additions to the sequence listings.

Amendment to the Priority Claim

The priority claim under 35 U.S.C. § 119(e) has been amended. Specifically, the specification has been amended on page 1, lines 3-4 to claim the benefit under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/098,235, filed August 28, 1998 and U.S. Application Serial No. 60/065,628, filed November 18, 1997.

The Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Claims 1-8 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

Claim 1 is drawn to a method for inactivating a gene introduced into the genome of a plant cell comprising, transforming the plant cell with a nucleic acid molecule comprising a promoter operably linked to a nucleotide sequence comprising the gene and introducing into the plant cell a chimeric oligonucleotide capable of recognizing and implementing a nucleotide conversion in the nucleic acid molecule. The Examiner asserts that the specification, while enabling for inactivating the AHAS gene and the PAT/GFP transgene in maize, does not reasonably provide enablement for a method of inactivating any integrated gene in the genome of any plant through the use of RNA-DNA chimeric oligonucleotides.

Applicants respectfully traverse. The Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation needed to practice the invention is not undue. *In re Wands*, 8 USPQ2d 1400 (Fed Cir 1988). Furthermore, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. *Id.*

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Office Action draws the conclusion for lack of enablement based on the analysis of four of the above mention Wand's Factors. Each of the Examiner's concerns as they relate to the identified Wands Factors is set forth below.

(I) The Predictability or Unpredictability of the Art

First, the Examiner states that there is "known unpredictability associated with the ability to predict the ability or efficacy of an RNA-DNA chimeric oligonucleotide to successfully target and inactivate any previously integrated gene in any plant" (page 4, lines 18-20, Office Action mailed April 9, 2002). The Examiner has broadly asserted the "known unpredictability" of the use of chimeric oligonucleotides to target and inactivate genes in a plant, but has failed to provide specific evidence of the unpredictability of the art. The Examiner is reminded that to establish a *prima facie* case of nonenablement, the Examiner must provide evidence of a rational basis as to why the disclosure does not teach the manner and process of making and using the invention to one of skill in the art without undue experimentation. Applicants respectfully submit that the Examiner has failed to satisfy this burden. Specifically, the Examiner has not provided evidence of the unpredictability of the use of chimeric oligonucleotides to target and modifying genes in a plant. See MPEP 2164.04. The Examiner is respectfully requested to provide an explanation of the "known predictability". Furthermore, if the Examiner's rejection is based on personal knowledge, Applicants respectfully request that the Examiner provide an affidavit under 37 CFR 1.104(d)(2) supporting the rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph.

(II) The Amount of Guidance Presented in the Specification

The Examiner asserts that the specification does not provide sufficient guidance for a method of inactivating any integrated gene through the introduction of RNA-DNA chimeric oligonucleotides. Specifically, the Examiner asserts that the specification "fails to teach the successful inactivation of any and/or all genes introduced into the genome of any and/or all plants comprising the administration of RNA-DNA chimeric oligonucleotides." (Page 4, lines

11-13, Office Action mailed April 9, 2002). This is an improper standard. "It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed". *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

In the instant case, independent claim 1 and its dependant claims recite a method for inactivating a gene introduced into the genome of a plant cell using a chimeric oligonucleotide. Dependant claim 5 and 22 recite the gene is a herbicide resistance gene. Dependant claims 9 and 10 recite the herbicide resistance gene is AHAS and EPSPS. And, dependant claims 13-15 recite the method occurs in a monocot, a maize plant, and a dicot, respectively. Applicants submit that the specification does provide sufficient guidance to enable the invention as broadly as it is claimed.

First, the specification provides in Figures 1-10, examples of ten chimeric oligonucleotides that are designed to produced predetermined alterations in the EPSP nucleotide sequence and result in herbicide resistance. In addition, Figures 11-12 provide examples of chimeric oligonucleotides designed to produce predetermined alterations in the AHAS gene that result in herbicide resistance. Example 1 demonstrates the successful *in vivo* targeting of the AHAS gene using the chimeric oligonucleotides shown in Figures 11 and 12. See, for example, Table 1 and 2. The PAT/GFP transgene was also successfully targeted *in vivo* using the chimeric oligonucleotides of the invention. See, for example, Table 1 and 2. The data demonstrates that the methods of the claimed invention result in frequencies of site-specific targeting in plants by chimeric oligonucleotides occurring at least 100 fold higher than by spontaneous mutation.

Second, the specification provides additional guidance regarding the design and synthesis of chimeric oligonucleotides that would enable one of skill in the art to make appropriate chimeric oligonucleotides. Specifically, the specification indicates that the chimeric oligonucleotides of the claimed invention "are designed as a single molecule, with two sequences that are inverted and complementary, capable of folding back on itself to form a duplex structure" (page 7, lines 29-31). The specification further provides that the chimeric

oligonucleotide comprises a modifying sequence of DNA, which has at least one mismatch to the target sequence, flanked by two sequence-specific targeting segments that are homologous to the target gene. One of skill in the art could readily identify sequences that are capable of forming a duplex as well as sequences that are homologous to the gene of interest.

One skilled in the art could also use well-known, standard mutagenesis techniques to identify desirable alterations in and thereby design an appropriate DNA modifying sequence. Moreover, many mutations, both dominant and recessive, in various herbicide resistance genes are already known and characterized in the art. In view of the disclosure in the specification, one of skill in the art could easily identify known mutations in a gene of interest that effect the activity of the polypeptide in a desired manner and subsequently design chimeric oligonucleotides that would alter the plant sequence accordingly. Accordingly, the specification provides sufficient guidance to one of skill to determine the alterations in the target sequence that will produce a protein or polypeptide conferring the desired activity.

And finally, routine assays for assessing whether a target gene has been inactivated are also known in the art. Page 25 of the specification demonstrates that the alteration in the target sequence of interest can include an alteration that produces a desired effect on the activity of the polypeptide encoded by the targeted sequence and thereby allows it to be phenotypically selectable. The alteration, however, can further include a change in the target sequence that, while not altering the amino acid sequence, does add or remove a restriction site. For instance, the example on page 25 of the specification demonstrates *in vivo* mutagenesis using a chimeric oligonucleotide designated AHAS621. This oligonucleotide was effective at altering both the function of the AHAS polypeptide and destroying a BfaI site. The Applicants have therefore demonstrated that RFLP allowed for an effective screen for the alteration of target sequence. Using a similar approach, Southern blot analysis could be used to identify the alteration in the sequence.

The specification therefore provides, in the form of illustrative example and terminology, sufficient guidance to one of skill in the art regarding how to generate the chimeric oligonucleotide and how to assay for determining whether a target gene has been inactivated.

(III) The Presence or Absence of Working Examples

The Examiner further concludes "one skilled in the art would not accept on its face the examples given in the specification of the successful targeting and inactivation of the previously characterized AHAS target gene in maize as being correlative or representative of the successful targeting and inactivation of any and/or all integrated genes in any and/or all plants" (page 4, lines 13-16, Office Action mailed April 9, 2002). Again, the Examiner appears to be simply discounting the working examples provided in the specification and making a broad assertion regarding hypothetical conclusions that would be rendered by one of skill in the art.

Applicants have provided specific working examples of the claimed invention. The Examiner's attention is drawn to Example 2 of the specification that demonstrates the successful inactivation of both the maize AHAS gene and a PAT/GFP transgene via the introduction of chimeric oligonucleotides. The specification also provides a detailed prophetic experimental procedure for designing, synthesizing, and introducing chimeric oligonucleotides directed to the introduction of a mutation in a maize EPSPS gene. See Example 1.

Prior to the present invention it was not known that the chimeric oligonucleotides recited in the pending claims could be used to target and inactivate a herbicide resistance gene in a plant as claimed by the instant invention. As demonstrated in the specification, plant genes can be successfully modified at the nucleotide level with a high degree of precision, by using chimeric oligonucleotides. As discussed above, the specification provides ample disclosure regarding how to target other genes in plants. Consequently, absent evidence to the contrary, one of skill in the art would accept that the specification provides sufficient guidance to make and use the claimed invention.

(IV) The Quantity of Experimentation Necessary

The Examiner states that the breadth of the claims requires undue experimentation to practic th invention. Specifically, the Examiner states that the "quantity of experimentation required to practice the invention would require the *de novo* determination of accessible target

sites, modes of delivery and formulations to target appropriate cells and/or tissues harboring any and/or all previously integrated target genes in any and/or all plants, whereby said gene is inactivated" (page 5, lines 9-13, Office Action mailed April 9, 2002). The Examiner is reminded that the Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation needed to practice the invention is not undue. *In re Wands,* 8 USPQ2d 1400 (Fed Cir 1988). Furthermore, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. *Id.*

Applicants stress that when evaluating the quantity of experimentation required, the court looks to the amount of experimentation required to practice a single embodiment of the invention, rather than the amount required to practice every embodiment of the invention. For example, in *Wands*, the claims at issue were drawn to immunoassay methods using any monoclonal antibody having a binding affinity for HbsAg of at least 10^{-9} M. The PTO had taken the position that the claim was not enabled as it would take undue experimentation to make the monoclonal antibodies required for the assay. The Federal Circuit reversed, and held that the claims were enabled, as the amount of experimentation required to isolate monoclonal antibodies and screen for those having the correct affinity was not undue. *Id.* Clearly, the Federal Circuit did not contemplate that every antibody useful in the methods of the claim must be identified. Rather, the court considered the amount of experimentation required to identify one or a few monoclonal antibodies having the required affinity. *See also Johns Hopkins University v. Cellpro*, 931 F. Supp. 303, 324 (D. Del. 1996), *aff'd in part, vacated in part, & remanded*, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998) ("The specification need only enable one mode of making the claimed invention.").

In the instant case, the Examiner first asserts that the determination of accessible target sites requires undue experimentation. Applicants respectfully disagree. First, as evidence that determination of target sites is routine and not undue, Applicants have successfully identified accessible target sites in a PAT/GFP and an AHAS gene and have demonstrated the targeting of a predetermined alteration in each of these genes through the administration of chimeric

oligonucleotides. It should be further noted that two transformant lines containing the PAT/GFP sequences were modified. See example 2, page 27-28. As indicated on page 28, lines 1-5, the chimeric oligonucleotides successfully targeted the transgenes when inserted into two independent positions in the genome. Similarly, the AHAS gene was also successfully targeted. Second, as discussed above, the specification provides specific guidance as to the identification of target sites in the EPSPS and AHAS genes, and moreover provides general strategies for determining appropriate target sites in other genes. See, for example, page 11, lines 22-29 and page 22, lines 3-23 of the specification.

And third, one skilled in the art could also use well-known, standard mutagenesis techniques to identify alterations in the target gene that would render it inoperable and thereby design an appropriate DNA modifying sequence. In addition, the Examiner is reminded that many mutations, both dominant and recessive, in various genes are already known and characterized in the art. In view of the disclosure in the specification, one of skill in the art could easily identify known mutations in a gene of interest that effect the activity of the polypeptide in a desired manner and subsequently design chimeric oligonucleotides that would alter the plant sequence accordingly.

In conclusion, as the target sequence is known and the screening methods are adequately described in the specification, the synthesis and screening of chimeric oligonucleotides is nothing more than routine experimentation analogous to the hybridoma screening the Federal Circuit found acceptable in *In re Wands* (858 F.2d 731,8 USPQ 1400(Fed. Cir. 1988)).

The Examiner further asserts that determination of the "modes of delivery and formulations to target appropriate cells and/or tissues harboring any and/or all previously integrated target genes" would require undue experimentation (page 5, lines 11-12, Office Action mailed April 9, 2002). It is unclear to Applicants what the Examiner is specifically addressing with this statement. Applicants have assumed that by "modes of delivery and formulations" the Examiner is referring to the introduction of the chimeric oligonucleotide into the nucleus of a plant cell.

The specification and the art provide routine methods for the introduction of oligonucleotides into the nucleus of a plant cell. See, for example, page 10, lines 15-34, page 11, lines 1-8, Example 1, particularly pages 13-16, and Example 2, particularly pages 19-20. In addition, the Examiner's attention is drawn to page 21, lines 19-30 of the specification that demonstrates the successful delivery of the chimeric oligonucleotide to both onion epidermis and maize cells. Therefore, given the guidance in the specification and the level of skill in the art, the amount of experimentation required to determine the "modes of delivery and formulations" is routine, not undue.

The Examiner further asserts that the determination of the factors necessary to target and inactivate a particular gene using chimeric oligonucleotides is "highly unpredictable" and, thus, would require undue experimentation. As noted above, the Examiner has failed to provide specific evidence of the unpredictability of the use of chimeric oligonucleotides to target and inactivate genes in a plant. If the Examiner possesses information evidencing the unpredictability of the art, Applicants respectfully request that the Examiner provide such evidence. Absent evidence to the contrary, however, Applicants respectfully submit that one of skill in the art would accept the specification as enabling.

Prior to the present invention, the successful targeting and inactivation of a gene in a plant cell as claimed by the present invention had not been shown. Applicants successfully determined accessible target sites and modes of delivery and formulations to target appropriate cells harboring previously integrated EPSPS, AHAS, and PAT/GFP genes. Thus, contrary to the Examiner's broad assertions of unpredictability in the art, Applicants respectfully submit that the experimentation required to practice the claimed invention is routine, not undue.

In view of the above arguments, Applicants respectfully request that the rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, be withdrawn and Applicants respectfully request the rejection not be applied to the newly submitted claims.

In re: Baszczynski *et al.*
Appl. No.: 09/579,784
Filed: May 26, 2000
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Consideration Of Previously Submitted Information Disclosure Statement

It is noted that an initialed copy of the PTO Form 1449 that was submitted with Applicants' Information Disclosure Statement filed June 11, 2002 has not been returned to Applicants' representative with the Office Action. Accordingly, it is requested that an initialed copy of the Form 1449 be forwarded to the undersigned with the next communication from the PTO. In order to facilitate review of the references by the Examiner, a copy of the Information Disclosure Statement and the Form 1449 are attached hereto. Copies of the cited references were provided at the time of filling the original Information Disclosure Statement, and, therefore, no additional copies of the references are submitted herewith. Applicants will be pleased to provide additional copies of the references upon the Examiner's request if it proves difficult to locate the original references.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office, Examiner Zara at Fax No. 703-746-5193 on the date shown below. **Pamela Lockley** (Type or print name of person signing certification.) Pamela Lockley Signature October 15, 2002 Date	CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on October 15, 2002.

Version with Markings to Show Changes Made:

In the Specification

Please amend page 1, lines 3-4 of the specification as follows:

This application is a divisional of U.S. Application Serial No. 09/193,612, filed on November 17, 1998, which claims the benefit of U.S. Provisional Application Serial No.60/098,235 filed August 28, 1998 and U.S. Provisional Application Serial No. 60/065,628 filed November 18, 1997, all of which [is] are herein incorporated by reference.

Please amend page 4, lines 13-17 of the specification as follows:

Figure 1 provides a chimeric oligonucleotide comprising three intervening blocks of RNA residues for modification of the maize EPSPS gene to a herbicide resistant form of the gene by converting two nucleotides at each of two amino acid residues of the target sequence. The linear (SED ID NO: 1) and active forms of the oligonucleotide are provided. A fragment of the maize EPSPS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 22.

Please amend page 4, lines 18-22 of the specification as follows:

Figure 2 provides a chimeric oligonucleotide comprising three intervening blocks of RNA residues for modification of the maize EPSPS gene to a herbicide resistant form of the gene by converting one nucleotide at each of two amino acid residues of the target sequence. The linear (SEQ ID NO: 2) and active forms of the oligonucleotide are provided. A fragment of the maize EPSPS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 23.

Please amend page 4, lines 23-27 of the specification as follows:

Figure 3 provides a chimeric oligonucleotide comprising two intervening blocks of RNA residues for modification of the maize EPSPS gene to a herbicide resistant form of the gene by

converting two nucleotides at each of two amino acid residues of the target sequence. The linear (SED ID NO: 3) and active forms of the oligonucleotide are provided. A fragment of the maize EPSPS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 23.

Please amend page 4, lines 28-32 of the specification as follows:

Figure 4 provides a chimeric oligonucleotide comprising two intervening blocks of RNA residues for modification of the maize EPSPS gene to a herbicide resistant form of the gene by converting one nucleotide at each of two amino acid residues of the target sequence. The linear (SEQ ID NO: 4) and active forms of the oligonucleotide are provided. A fragment of the maize EPSPS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 23.

Please amend pages 4 and 5, lines 33-34 and 1-4, respectively, of the specification as follows:

Figure 5 provides a chimeric oligonucleotide comprising two intervening blocks of RNA residues for modification of the maize EPSPS gene to a herbicide resistant form of the gene by converting two nucleotides at each of two amino acid residues of the target sequence. The first amino acid residue target is within a DNA region while the second amino acid residue target is within an RNA region. The linear (SEQ ID NO: 5) and active forms of the oligonucleotide are provided. A fragment of the maize EPSPS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 22.

Please amend page 5, lines 5-10 of the specification as follows:

Figure 6 provides a chimeric oligonucleotide comprising two intervening blocks of RNA residues for modification of the maize EPSPS gene to a herbicide resistant form of the gene by converting one nucleotide at each of two amino acid residues of the target sequence. The first amino acid residue target is within a DNA region while the second amino acid residue target is

within an RNA region. The linear (SEQ ID NO: 6) and active forms of the oligonucleotide are provided. A fragment of the maize EPSPS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 24.

Please amend page 5, lines 11-16 of the specification as follows:

Figure 7 provides a chimeric oligonucleotide comprising two intervening blocks of RNA residues for modification of the maize EPSPS gene to a herbicide resistant form of the gene by converting two nucleotides at each of two amino acid residues of the target sequence. The first amino acid residue target is within an RNA region while the second amino acid residue target is within a DNA region. The linear (SEQ ID NO: 7) and active forms of the oligonucleotide are provided. A fragment of the maize EPSPS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 22.

Please amend page 5, lines 17-22 of the specification as follows:

Figure 8 provides a chimeric oligonucleotide comprising two intervening blocks of RNA residues for modification of the maize EPSPS gene to a herbicide resistant form of the gene by converting one nucleotide at each of two amino acid residues of the target sequence. The first amino acid residue target is within an RNA region while the second amino acid residue target is within a DNA region. The linear (SEQ ID NO: 8) and active forms of the oligonucleotide are provided. A fragment of the maize EPSPS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 24.

Please amend page 5, lines 23-27 of the specification as follows:

Figure 9 provides a chimeric oligonucleotide for a single amino acid modification of the maize EPSPS gene to a herbicide resistant form of the gene. The amino acid target here corresponds to the first of the two amino acid residues targeted by the chimeric oligonucleotides in Figures 1-8. The linear (SEQ ID NO: 9) and active forms of the oligonucleotide are provided.

A fragment of the maize EPSPS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 25.

Please amend page 5, lines 28-32 of the specification as follows:

Figure 10 provides a chimeric oligonucleotide for a single amino acid modification of the maize EPSPS gene to a herbicide resistant form of the gene. The amino acid target here corresponds to the second of the two amino acid residues targeted by the chimeric oligonucleotides in Figures 1-8. The linear (SEQ ID NO: 10) and active forms of the oligonucleotide are provided. A fragment of the maize EPSPS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 26.

Please amend pages 5 and 6, lines 33-34 and 1-2, respectively, of the specification as follows:

Figure 11 provides a chimeric oligonucleotide for a single amino acid modification at amino acid position 621 of the maize AHAS gene to a herbicide resistant form of the gene. The linear (SEQ ID NO: 11) and active forms of the oligonucleotide are provided. A fragment of the maize AHAS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 27.

Please amend page 6, lines 3-6 of the specification as follows:

Figure 12 provides a chimeric oligonucleotide for a single amino acid modification at amino acid position 165 of the maize AHAS gene to a herbicide resistant form of the gene. The linear (SEQ ID NO: 12) and active forms of the oligonucleotide are provided. A fragment of the maize AHAS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 28.

Please amend page 6, lines 7-10 of the specification as follows:

Figure 13 provides a chimeric oligonucleotide for a single nucleotide modification which converts a stop codon to a codon encoding tyrosine in a transgene target previously introduced into maize (see text). The linear (SEQ ID NO: 13) and active forms of the oligonucleotide are provided. A fragment of the maize AHAS amino acid sequence is translated beneath the active oligonucleotide and is set forth in SEQ ID NO: 29.

Please amend page 17, lines 12-28 of the specification as follows:

For the transgene target a translational fusion between phosphinothricin-N-acetyltransferase, *pat* (Wohlleben *et al.* (1988) *Gene 70*:25-37) and the green fluorescence protein, GFP (Prasher *et al.* (1992) *Gene 111*:229-233) was created. *pat* is a functional analog of the *bar* gene that similarly detoxifies Bialaphos. The coding sequences of GFP and *pat* have been modified to utilize maize preferred codons to enhance expression, these modified genes are referred to as GFPm and mo-PAT respectively. See, for example, U.S. application 09/003,287. A fusion was initially created by cloning the 3' BglII site in mo-PAT to a 5' flanking BamHI site on GFPm. Site directed mutagenesis (MORPH kit, 5'-3' Boulder, CO) was then used to remove the start codon (ATG) from GFPm to ensure low background expression of GFPm in target lines. Using the oligonucleotide PHN14593, 5'CGGTGACGCAGATCTATCCAACATTGTCCAAGGGC3' (SEQ ID NO: 14), the BglII site was recreated in mo-PAT and the start codon of GFPm was removed simultaneously. Four amino acids, YPTS, form the junction in the mo-PAT/GFPm sequence. The vector pPHP10699, is a positive control mo-PAT/GFPm fusion cloned under the control of the maize Ubiquitin-1 promoter and pinII terminator in a pUC-derived plasmid backbone.

Please amend pages 17 and 18, lines 29-34 and 1-6, respectively, of the specification as follows:

To create the target sequence for correction, the native *pat* stop codon (TGA) was inserted in the junction of mo-PAT/GFPm. Site-dir cted mutagenesis of pPHP10699 with oligonucleotide PHN16214, 5'GGTGACGCAGATCTAGGTACCATCGTCCAAGGGCGAG3'

(SEQ ID NO: 15), was used to change the junction sequence from YPTS to *VPS and to introduce a *KpnI* site adjacent to the stop codon. This creates a sequence that only expresses mo-PAT, but with correction to remove the stop codon, GFPm expression results. When making corrections to this target, changing the TAG stop codon to TAC also knocks out the *KpnI* site and creates a novel *Sna*BI site. The vector pPHP11207, contains the mo-PAT/TAG/GFPm target sequence, cloned with the maize Ubiquitin-1 promoter and pinII terminator, and inserted into a superbinary vector pSB1 for *Agrobacterium* mediated transformation of maize (Ishida *et al.* (1996) *Nature Biotech. 14*:745-750).

Please amend page 20, lines 16-30 of the specification as follows:

PCR amplification and sequence analysis - Target sequences were amplified from the extracted genomic DNA of putative events, by *Pwo* or *Taq* polymerase (Boehringer Mannheim, Indianapolis, IN) with 30 cycles of 35 seconds at 95°C, 35 seconds at 60°C, and 35 seconds at 72°C using a MJ thermocycler (MJ Research, Watertown, MA). For the AHAS621 target, primers common to both AHAS108 and AHAS109 were designed with the following sequences: 5'GCAGTGGGACAGGTTCTAT (PHN21971) (SEQ ID NO: 16) and 5'AGTCCTGCCATCACCATCCA (PHN21972) (SEQ ID NO: 17). For the AHAS165 target, the following primers were used: 5'ACCCGCTCCCCCGTCAT (PHN21973) (SEQ ID NO: 18) and 5'ATCTGCTGCTGGATGTCCTTGG (PHN21974) (SEQ ID NO: 19). For the moPAT/GFPm target, primers used were: 5'CGCAACGCCTACGACTGGA (PHN21976) (SEQ ID NO: 20) and 5'TGATGCCGTTCTTCTGCTTGTC (PHN21978) (SEQ ID NO: 21). PCR fragments were purified and either cloned (see below) or directly sequenced in both directions on an ABI 377 automated sequencer.

In the Claims

1. (Amended) A method to inactivate a gene introduced into a [plant] genome of a plant cell, said method comprising:

transforming said [organism] plant cell with a [transfer cassette] nucleic acid molecule comprising a promoter operably linked to a nucleotide sequence [encoding] comprising said gene; and

introducing into said plant cell at least one chimeric [RNA-DNA] oligonucleotide [molecule] said chimeric oligonucleotide having at least a first block of RNA residues, and a second block of RNA residues, wherein said first and said second blocks of RNA residues are homologous to said nucleic acid molecule and flank a block of DNA residues, said chimeric oligonucleotide being capable of recognizing and implementing a nucleotide conversion in said nucleic acid molecule [transfer cassette such that an interruption in the normal expression of said gene is created, thereby rendering said gene inoperable].

3. (Amended) The method of claim 1, wherein said nucleotide conversion is in the coding region of said gene.